The Evolution of Statistical Process Control Applied to Blood Product Manufacturing

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- Introduction
- General QC considerations
- Evolution of a statistical basis for QC using residual WBC contamination of leukoreduced blood components as an example
  - Non-statistical approaches
  - Binomial
  - Scan statistics

Allogeneic Blood Collection in the US

- Approximately 14 million whole blood collections/yr are processed into multiple components
  - red blood cells
  - platelets
  - plasma
- Apheresis procedures are also used to collect these components selectively.

Allogeneic Whole Blood Collection in the US

1002 licensed whole blood collection facilities

- collect 92% of the US blood supply
- distribute interstate

838 “registered-only” facilities (typically hospitals)

- collect 8% of blood supply
- tend to be lower volume operations
- distribute intrastate only (generally within facility)

Allogeneic Blood Collection in the US

- All blood and blood components
  - 21 CFR 211.160(b) ……"conform to appropriate standards of identity, strength, quality, and purity."
- Some blood components are modified further:
  - leukocyte reduced
  - irradiated
  - pooled (random donor platelets, AHF cryoprecipitate)
  - freezing/deglycerolization

Quality Control Testing–General Considerations

Why do it at all?

- Unexpected sub-optimal reagents or materials
- Unrecognized variation from validated procedures
- Proactive early identification of problems

Quality Control Testing–General Considerations

Why do it statistically?

- Permits a definition of product conformance to a standard with a given probability
- Facilitates the meaningful and efficient identification of non-conformance limits that trigger a need for action
- Allows QC testing to be customized to individual products
  - Different baseline levels of non-conformance
  - Different health impacts of product failure

Quality Control –General Considerations

FDA regulatory policy for Quality Control testing

- Serves as a minimal standard. Industry standards may be more stringent.
- Must define practical strategies for suitable for both very large and very small facilities.

Issue: Low Production Volume

- A large blood establishment may produce several hundred components per day by a variety of procedures.
- A small blood establishment that produces 100 components per week by four different procedures may have only 25 components per week available for QC testing.
- A very small registered facility may routinely produce blood components in numbers as low as n=10 per week

Quality Control –General Considerations

Local quality control procedures are defined by blood establishment Standard operating procedures (SOPs)

- For licensed establishments, SOPs are reviewed in Prior Approval License Supplements
- Compliance with SOPs is reviewed on inspection both pre- and post licensure for licensed firms, and biennially for registered, unlicensed firms

Unique Problems in QC of Blood and Blood Components for Transfusion

- Low volume production facilities have the least opportunity for statistical QC, but may need it the most due to infrequent use of procedures
- Each blood component is an individual lot. Therefore, labor and cost of QC are major factors in the practicality of testing (particularly if product is sacrificed).
- Some production variables (usually donor-related) cannot be controlled by current technology (e.g. occult bacteremia, HbS-related leukocyte reduction failure). These contribute to baseline non-conformance and are not process failures

The dilemma regarding QC of WBC removal by pre-storage leukoreduction

- FDA has always encouraged the use of pre-storage leukoreduction
- Leukoreduced products most likely have benefits for the general recipient population, but the cost-effectiveness of universal leukoreduction has been hotly debated and studies have been suggestive, but not compelling
- **Consider the dilemma is how to define a quality control strategy that does not inhibit the use of leukoreduction, but provides rigorous QC for patient subpopulations where WBC removal is vital (e.g CMV susceptible patients)?

Evolution of a Conceptual Framework for Statistical Process Control (SPC) for Biological Products

Quality Control Factors to consider

- 100% product qualification vs. sampling
  - How critical is final product specification?
- Appropriate distributions
  - dichotomous vs. continuous outcome
  - log-normal distribution?
- One vs. two tail
  - (automobile piston vs. WBC count)
- Frequency of QC cycle
  - How long can out-of-control process be tolerated?

Evolution of a Conceptual Framework for Statistical Process Control (SPC)

I. "Population testing" (aka 100% Quality Control)*

- apheresis platelet counts
- platelet bacterial contamination - AABB standard
- leukoreduced products for CMV- susceptible patients (proposed in LR draft guidance January, 2001)

* Product release testing is a subset

100% Quality Control
WBC removal

Advantages:

- 100% of labeled LR products will meet product standard
- Reduces inappropriate WBC exposure to susceptible patient sub-populations (e.g. CMV susceptible)
- Stimulates new technologies that will facilitate cost-effective WBC enumeration.

Disadvantages:

- Manual counts are very labor intensive
- Limited selection of automated counting devices
- Blood centers may ultimately choose to provide fewer leukoreduced products.

Evolution of a Conceptual Framework for Statistical Process Control (SPC)

II. "Sample"-based quality control without a statistical framework

e.g evaluate 1% of representative products (or at least n=4/month for facilities producing <400 units per month).

– Current practice for most blood component process control

Current Process Control Recommendations- Pre-storage Leukoreduction

1996 Memo:

Evaluate 1% of representative products (or at least n=4/mo.)

$< 5 \times 10^6$ residual and 85% retention of original RBC content

$<8.3 \times 10^5$ residual WBC and 85% retention of platelets ($<5 \times 10^6$ platelets, pheresis)

All evaluated products must meet specs, if failure observed label must be revised and process investigated.

WBC counting methods: Nageotte, Flow, other validated methods

"Sample"-based quality control without a statistical framework

- Advantages
  - Simple, may offer low cost
  - Staff training is straightforward
- Disadvantages
  - Lack of rigor may allow non-conforming products to be produced for an extended period without detection (may lead to public health impact, large recalls/market withdrawals, targeted FDA inspection)
  - Sampling scheme defined may actually be unnecessarily large

Binomial approach to SPC

- Pre-defined independent random sample clusters are tested over a pre-defined time period with pre-established failure levels.

- Considers:
  - Background levels of non-conformance
  - Statistical parameters of the control strategy
  - Minimal acceptable time within which to detect a series of non-random process failures (safety)

Binomial approach to SPC

Examples of sample size and maximum # of failed tests expected (at 95% confidence) for a conforming process

Failure rate allowed	QC sample size	Max # failed tests
10%	NA	
5%	59	0
5%	93	1
5%	124	2
1%	299	0
1%	471	1
0.5%	598	0
0.5%	947	1

Binomial approach to SPC for WBC removal

Leukoreduction draft guidance January, 2001

- Binomial SPC to assure with 95% confidence that 95% of leukocyte reduced products meet the product standard.
  - 95% conformance - safe and pure product
  - 95% CI is accepted scientific norm

  ($p<.05$ that chance non-conformance will exceed 5%)

- Compatible with ISBT Working Group recommendations

Binomial approach to statistical QC for WBC removal (cont.)

(Leukoreduction draft guidance January, 2001)

- Process validation = 60 consecutive WBC counts
- Ongoing QC = 1% of total production (but not less than random 5 counts per week/60 counts per quarter).
- Binomial SPC criteria can be met by testing n=60 without failure, or n=93 with one failure, or n=124 with two failures….
- QC failure requires consecutive counts of next 60 units
  - 0/60 consecutive - resume normal QC
  - ≥ 1/60 consecutive - out of control process/ investigation

Binomial approach to statistical QC for WBC removal (cont.)

Leukoreduction draft guidance January, 2001)

- Exact binomial distribution, single tail
  - Does not require log-normal distribution
- WBC Counts can be “pass/fail”
- Alternate, equivalent SOPs within defined statistical parameters may be acceptable
  - Normal/Log normal distribution may be necessary
  - Alternate approaches reviewed by CBER as PAS

Advantages and Disadvantages of Binomial Approach

Advantages

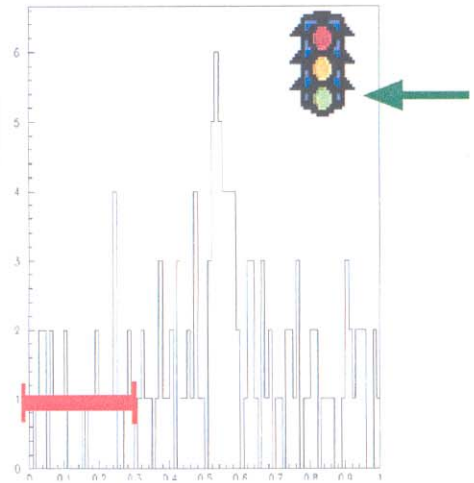
- Defines parameters of product conformance
- Conceptually feasible (FDA)
- Assures that 95% of products labeled as "leukocytes reduced" will meet the product standard with 95% confidence.

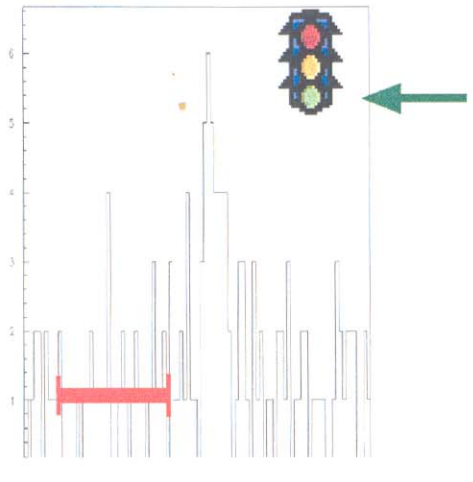
Disadvantages

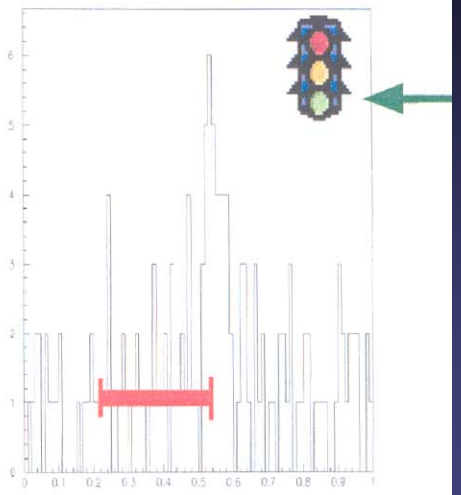
- Occasional products with levels of residual WBCs that exceed the product standard may unknowingly be transfused to CMV-susceptible patients.
- The QC strategy proposed may be complex and contribute to reduced compliance. Operational feasibility questioned by industry
- “Clusters” of failures at end points may be masked

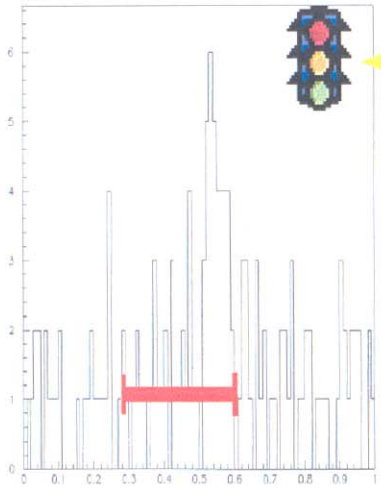
Scan Statistics

- Identifies “clusters” of events in time and space
  - many product failures are non-random
    - bad reagent or soft goods
    - faulty machine or software
    - staff errors
- Uses a rolling window of test results for non-conformance assessment









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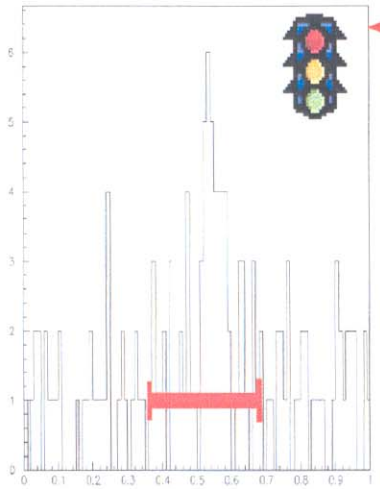

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S(w) is the largest number of events in a running window of fixed length w (⟷)

S(w) ≡ Scan Statistics

Scan Statistics -

Probability that at least k events are observed is:

$$\mathbf{P(S \geq k) = 1 - Q_L}$$

Probability of detecting out of control sample when probability is increased by a factor of δ is:

$$\mathbf{P(S \geq k|}\ \delta p) = 1\text{-}B(k,m,\delta p\mathbf{)} + \frac{\mathbf{2 *}\ b(k,m,\delta p)}{\Theta\text{-}1} - \frac{b(k+1,m,\delta p)}{\Theta^2}$$

Scan Statistics -

N = # of tests

m = window size

k = observed failures

p = probability of one obs failure

P = probability of 2 or more failures

Delta = threshold (3x, p, 5x p…. etc)

Power = Power to detect Delta within m

Scan Statistics -
e.g. Process control - Residual WBC

N	m	k	p	P	Power	
# **tests**	wdw size	obs failures	p 1 fail	p 2 more fail to detect	$\delta = 3$	$\delta = 5$
1200	233	2	0.005	0.049	0.84	0.95

Translation: We are counting a moving window of n=233 within a group of 1200 tests. When observing a second failure in our window, we would be detecting an overall failure rate at 3x baseline with 84% power with no more than a 5% chance of falsely determining an in-spec process to be out of spec.

Example

Let's say that 24,000 Platelets, Pheresis are collected per year at your blood center.

- Test ~2,400 per year
- Random selection from total collections
- For this example, calculations use a "window" of 120 tests
  - 3 failures in the 120 test "window" would trigger an investigation of an unacceptable level of non-conformance
  - The false positive rate would be 4%

How Does This Work?

- For this example, let's say you perform 10 tests on any given day
- Start the rolling sample window of 120 tests.
  - As long as you have < 3 failures, the level of non-conformance for the process is considered to be acceptable.
  - After 120 tests are complete, the window "rolls" forward and the next 120 tests now include the testing of the samples from days 2-12, and a new set of 10 samples; those tested on the 13th day.

continued

First 120

Test day	1	2	3	4	5	6
Tests	10	20	30	40	50	60
Failures	0	0	0	1	0	0

Test day	7	8	9	10	11	12
Tests	70	80	90	100	110	120
Failures	0	0	1	0	0	0

continued

Second 120

Test day	2	3	4	5	6	7
Tests	10	20	30	40	50	60
Failures	0	0	1	0	0	0

Test day	8	9	10	11	12	13	
Tests	70	80	90	100	110	120	**X**
Failures	0	1	0	0	0	1	

continued

- In the event of QC failure (trigger reached):
  - A complete failure investigation should be initiated
    - Donor-related? (may be non-process)
    - Technical/Operator error/SOP adherence
    - Filter related performance: lot number
    - Sampling
    - Cell counting methodology
    - Manufacturer contact

continued

- Corrective action and follow-up should be performed:
  - If resolved, QC should be re-initiated
    - The count of tests restarts at 0 (or day 1)
  - If not resolved, revalidation performed as appropriate

Summary

- Process control for blood components is complex and often consists of trying to detect rare nonconformance events with small samples.
- Current thinking is that in the future, FDA will recommend statistical parameters for process control where appropriate
  - FDA will provide an acceptable procedure (in user-friendly format)
  - Alternate QC approaches will be considered that meet the defined parameters

References

- Glaz J, Naus J, Wallenstein S. Scan Statistics 2001. Springer Publishing.

- Lachenbruch PA, Foulkes MA, Williams, AE, Epstein JS. Potential use of the scan statistic in the quality control of blood products J Pharm Statistics 15:353-366, 2005